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Qishou Xu

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26530 7590 07/01/2009  
LADAS & PARRY LLP  
224 SOUTH MICHIGAN AVENUE  
SUITE 1600  
CHICAGO, IL 60604

EXAMINER

GOON, SCARLETT Y

ART UNIT

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1623

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/522,110	<b>Applicant(s)</b> XU ET AL.	
	<b>Examiner</b> SCARLETT GOON	<b>Art Unit</b> 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 March 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,6-8,12 and 21-32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,6-8,12 and 21-32 is/are rejected.
- 7) ☒ Claim(s) 22-32 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6 March 2009 and 8 June 2009</u> .                            | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6 March 2009 has been entered.

This Office Action is in response to Applicants' Amendment and Remarks filed on 6 March 2009 in which claims 2-5, 9-11 and 13-20 were cancelled, claims 1 and 12 are amended to change the scope and breadth of the claims, claims 6 and 7 are amended for clarity, and new claims 21-32 are added.

Claims 1, 6-8, 12 and 21-32 are pending in the instant application and are examined on its merits herein.

The statement regarding the allowability of claims 6-8 if written in independent form, indicated in the Office Action dated 23 December 2008, is herein withdrawn (for reasons indicated below).

***Priority***

This application is a National Stage entry of PCT/CN03/00609 filed on 29 July 2003 and claims priority to China foreign application 02125917.8 filed on 2 August 2002. A certified copy of the foreign priority document in Chinese has been received. No English translation has been received.

***Information Disclosure Statement***

The information disclosure statements (IDS) dated 6 March 2009 and 8 June 2009 comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, they have been placed in the application file and the information therein has been considered as to the merits.

***Objections Withdrawn***

Applicant's amendment, filed 6 March 2009, with respect to the objection of claim 1 for misspelling "monoester" is persuasive because the amendment has deleted the word "monester".

In view of the cancellation of claims 9-11, all objections made with respect to claims 9-11 in the previous Office Action are withdrawn.

These objections have been **withdrawn**.

***Rejections Withdrawn***

Applicant's amendment and remarks, filed 6 March 2009, with respect to the rejection of claims 1 and 9-12 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention with respect to the recitations "derivative" and "isobutyrate of riboflavin," have been fully considered and is persuasive because the claim as amended deletes the said recitations.

Applicant's amendment and remarks, filed 6 March 2009, with respect to the rejection of claim 12 under 35 USC § 112, second paragraph, as being incomplete for omitting essential steps, have been fully considered and is persuasive because the claim as amended specifically indicates what steps are required for treatment of the indicated condition.

Applicant's amendment and remarks, filed 6 March 2009, with respect to the rejection of claim 12 under 35 USC § 112, first paragraph, for lack of scope of enablement, have been fully considered and is persuasive because the claim has been amended to more specifically claim matter enabled by the disclosure, namely the compound of formula (II) and its use in a method of treating ariboflavinosis, digestive tract catarrh and persistent oral ulcer in an animal.

Applicants' amendment and arguments, filed 6 March 2009, with respect to the rejection of claim 1 under 35 USC § 103(a) as being unpatentable over Edwards *et al.*, have been fully considered and are persuasive because Edwards *et al.* do not teach or fairly suggest the compound of amended claim 1. The riboflavin compounds taught by

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Edwards *et al.* are tetra-acylated while the riboflavin compound instantly claimed by Applicant is mono-acylated with a lauric residue.

Applicants' amendment and arguments, filed 6 March 2009, with respect to the rejection of claim 12 under 35 USC § 103(a) as being unpatentable over Edwards *et al.* as applied to claim 1, further in view of Okuda *et al.*, have been fully considered and are persuasive. Since Edwards *et al.* do not teach or fairly suggest the compound of amended claim 1, a method of treating ariboflavinosis, digestive tract catarrh and persistent oral ulcer in an animal comprising administration of the compound of claim 1 cannot be obvious.

In view of the cancellation of claims 9-11, all rejections made with respect to claims 9-11 in the previous Office Action are withdrawn.

These rejections have been **withdrawn**.

### ***Claim Objections***

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

The use of Claim 22 is duplicated and encompasses two different subject matters. Appropriate correction is required.

The following are new grounds of rejections.

***Claim Rejections - 35 USC § 112, Second Paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation “DA (daunorubicin, cytosine arabinoside)” in the claim renders the claim herein indefinite. It is unclear whether daunorubicin and cytosine arabinoside are examples of DA or a requirement of the claim limitation. It would appear that DA is an abbreviation for daunorubicin (although it is not indicated in the Specification as being such) and thus it should be represented in the claim as “daunorubicin (DA),” but it still remains unclear what is the role of cytosine arabinoside in the claim.

***Claim Rejections - 35 USC § 112, First Paragraph***

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment with respect to the amended claims herein has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for "cytosine arabinoside" in a chemotherapy regimen. The original specification clearly discloses "CODPL, HDMTX, DA" in paragraph 0051 of the published application. However, cytosine arabinoside is not disclosed in the specification as originally filed. Adequate written description means that, in the specification, the applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the [claimed] invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 [19 USPQ2d 1111] (Fed. Cir. 1991). When no such description can be found in the specification, the only thing the PTO can reasonably be expected to do is point out its nonexistence. *In re Alton*, 76 F.3d 1168, 1175 [37 USPQ2d 1578] (Fed. Cir. 1996).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

### **Section [0001]**

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record).

Yamabe *et al.* teach the preparation of riboflavin trilaurate (abstract).

The teachings of Yamabe *et al.* differ from that of the instantly claimed invention in that Yamabe *et al.* teach a trilaurate ester of riboflavin whereas the claims of the instant invention is drawn to a 5'-laurate monoester of riboflavin.

Okuda *et al.* teach nutritional and ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate. To test the nutritional effects of the riboflavin derivatives, rats were fed either a standard diet, a riboflavin-deficient diet, a riboflavin-deficient diet supplemented with riboflavin-5'-monobutyrate suspended in olive oil, or a riboflavin-deficient diet supplemented with riboflavin-5'-monopalmitate suspended in olive oil (p. 9, under subheading "methods"). The authors previously showed that riboflavin tetrabutryate had the same vitamin B<sub>2</sub> activity (nutritional and ariboflavinosis-curing effects) in young rats as riboflavin, but riboflavin tetrapalmitate did not have vitamin B<sub>2</sub> activity as rats administered riboflavin tetrapalmitate clearly showed ariboflavinosis. Similar to riboflavin tetrabutryate, rats fed a diet supplemented with riboflavin-5'-monobutyrate exhibited vitamin B<sub>2</sub> activity (p. 13, second full paragraph). However, rats fed a diet supplemented with riboflavin-5'-monopalmitate showed signs of lower vitamin B<sub>2</sub> activity. Their results suggest that riboflavin-5'-monobutyrate is easily hydrolyzed to riboflavin, and hence has the same nutritional effect as riboflavin, while riboflavin-5'-monopalmitate was only slowly hydrolyzed to riboflavin (p. 13, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate,

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with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrates and riboflavin tetrapalmitate. Since Okuda *et al.* teach that riboflavin tetrapalmitate did not have vitamin B<sub>2</sub> activity as compared to riboflavin tetrabutyrates when fed to rats while riboflavin-5'-monopalmitate showed signs of lower vitamin B<sub>2</sub> activity as compared to riboflavin-5'-monobutyrate when fed to rats, one would have been motivated to modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-laurate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Okuda *et al.*, that long chain tetra-esters of riboflavin exhibited no riboflavin activity while long chain mono-esters of riboflavin exhibited some riboflavin activity. Therefore, since Okuda *et al.* also teach that the tetra- and mono-butyrate esters of riboflavin showed the same activity as riboflavin, suggesting that shorter alkyl chain esters of riboflavin are better hydrolyzed, one would have been motivated to shorten the palmitate chain to a laurate chain, such as that taught by Yamabe *et al.* However, one would further modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-monolaurate, as the teachings of Okuda *et al.* also suggests that with longer chain esters, the mono-ester compound is better hydrolyzed as compared to the tetra-ester compound, and therefore, would also likely be better hydrolyzed as compared to the tri-ester compound taught by Yamabe *et al.*

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

**Section [0002]**

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record) as applied to claim 1 above, further in view of Remington's The Science and Practice of Pharmacy (PTO-892, Ref. U), in view of journal publication by Stuchlík *et al.* (PTO-892, Ref. V), as evidenced by online publication entitled "Carrier/Fixed Oil Profiles" (PTO-892, Ref. W).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

Yamabe *et al.* and Okuda *et al.* do not teach a composition of riboflavin esters that comprise ethyl oleate.

Remington teaches different diluting agents (vehicles or carriers) that are used as solvents for active medicinals. Remington further indicates that prescribers have the opportunity to make their own prescriptions more acceptable to the patient since a large selection of diluting agents is available in a choice of colors and flavors (p. 1027).

Stuchlík *et al.* teach different vegetable oils, animal fats, and oils of natural origin that are commonly used as carriers in pharmaceutical formulations (p. 20, column 2, subheading "Potential Carriers" and Table 5). As shown on Table 7 (p. 21), the main composition of olive oil is oleic acid. As evidenced by the online publication entitled "Carrier/Fixed Oil Profiles," camellia oil has a very high content of oleic acid.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrates and riboflavin tetrapalmitate, with the teachings of Remington, regarding the different diluting agents available for use in medicinals, with the teachings of Stuchlík *et al.*, regarding different vegetable oils used as pharmaceutical carriers. Since Okuda *et al.* teach that riboflavin tetrapalmitate did not have vitamin B<sub>2</sub> activity as compared to riboflavin tetrabutyrates when fed to rats while riboflavin-5'-monopalmitate showed signs of lower vitamin B<sub>2</sub> activity as compared to riboflavin-5'-monobutyrate when fed to rats, one would have been motivated to modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-laurate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Okuda *et al.*, that long chain tetra-esters of riboflavin exhibited no riboflavin activity while long chain mono-esters of riboflavin exhibited some riboflavin activity. Therefore, since Okuda *et al.* also teach that the tetra- and mono-butyrate esters of riboflavin showed the same activity as riboflavin, suggesting that shorter alkyl chain esters of riboflavin are better hydrolyzed, one would have been motivated to shorten the palmitate chain to a laurate chain, such as that taught by Yamabe *et al.* However, one would further modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-monolaurate, as the teachings of Okuda *et al.* also suggests that with longer chain esters, the mono-ester compound is better hydrolyzed as compared to the tetra-ester compound, and

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therefore, would also likely be better hydrolyzed as compared to the tri-ester compound taught by Yamabe *et al.*

With regards to the combination of ethyl oleate in the composition, since Remington teaches that a variety of diluting agents can be added to medicinals and further indicates that prescribers have the opportunity to make their own prescriptions more acceptable to the patient since a large selection of diluting agents is available in a choice of colors and flavors, it would have been *prima facie* obvious for one of ordinary skill in the art to determine which carrier would be most appropriate for use in their composition depending on the compound's properties, intended mode of administration of the composition, and intended patient population.

With regards to the combination of camellia oil in the composition, since Stuchlík *et al.* teach that olive oil and camellia oil is often used as a carrier in pharmaceutical formations and that the main components of olive oil and camellia oil are both oleic acid, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the olive oil in the riboflavin ester composition taught by Okuda *et al.* with camellia oil and still obtain similar predictable results. Furthermore, it is considered within the capabilities of one of ordinary skill in the art to optimize the amounts of diluting agent/carrier in the composition to obtain the most effective formulation.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

**Section [0003]**

Claims 12, 24, 25, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record), in view of Remington's The Science and Practice of Pharmacy (PTO-892, Ref. U).

The teachings of Yamabe *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Yamabe *et al.* differ from that of the instantly claimed invention in that Yamabe *et al.* teach a trilaurate ester of riboflavin whereas the claims of the instant invention is drawn to a 5'-laurate monoester of riboflavin. Furthermore, Yamabe *et al.* do not teach that the trilaurate ester of riboflavin is in a composition with ethyl oleate.

The teachings of Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103.

The teachings of Remington were as described above in section [0002] of the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutryate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the different diluting agents available for use in medicinals. Since Okuda *et al.* teach that riboflavin tetrapalmitate did not have vitamin B<sub>2</sub> activity as compared to riboflavin tetrabutryate

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when fed to rats while riboflavin-5'-monopalmitate showed signs of lower vitamin B<sub>2</sub> activity as compared to riboflavin-5'-monobutyrate when fed to rats, one would have been motivated to modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-laurate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Okuda *et al.*, that long chain tetra-esters of riboflavin exhibited no riboflavin activity while long chain mono-esters of riboflavin exhibited some riboflavin activity. Therefore, since Okuda *et al.* also teach that the tetra- and mono-butyrate esters of riboflavin showed the same activity as riboflavin, suggesting that shorter alkyl chain esters of riboflavin are better hydrolyzed, one would have been motivated to shorten the palmitate chain to a laurate chain, such as that taught by Yamabe *et al.* However, one would further modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-monolaurate, as the teachings of Okuda *et al.* also suggests that with longer chain esters, the mono-ester compound is better hydrolyzed as compared to the tetra-ester compound, and therefore, would also likely be better hydrolyzed as compared to the tri-ester compound taught by Yamabe *et al.*

With regards to the combination of ethyl oleate in the composition, since Remington teaches that a variety of diluting agents can be added to medicinals and further indicates that prescribers have the opportunity to make their own prescriptions more acceptable to the patient since a large selection of diluting agents is available in a choice of colors and flavors, it would have been *prima facie* obvious for one of ordinary skill in the art to determine which carrier would be most appropriate for use in their

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composition depending on the compound's properties, intended mode of administration of the composition, and intended patient population.

With regards to the administration of the riboflavin ester to a human, as Okuda *et al.* teach *in vivo* administration of the compounds to rats, it would have been *prima facie* obvious to one of ordinary skill in the art to apply the method to humans after optimization in rats.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

#### **Section [0004]**

Claims 21-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record), in view of Remington's The Science and Practice of Pharmacy (PTO-892, Ref. U) as applied to claims 12, 24, 25, 28 and 29, further in view of PG Pub No. US 2003/0105104 A1 by Burzynski (of record), in view of journal publication by McCarthy *et al.* (of record).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103. The teachings of Remington were as described above in section [0002] of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.*, Okuda *et al.* and Remington differ from that of the instantly claimed invention in that the riboflavin ester is administered for

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treatment of ariboflavinosis and not for the treatment of digestive tract catarrh caused by bone marrow transplantation, leukemia or chemotherapy.

Burzynski teaches a pharmaceutical composition comprising riboflavin, effectors of the urea cycle, and amino acids, suitably combined with appropriate carriers, diluents, or excipients (abstract; paragraph 0001 and 0008; claim 14), as well as a method for alleviating or reducing the toxic, nutritional and metabolic disturbances associated with cancer and cancer chemotherapy by administering the said composition to a cancer patient in need thereof (paragraph 0024; claim 1). Common side effects associated with cancer treatment include tiredness, loss of appetite, mucositis, diarrhea and myelosuppression (paragraph 0072). In example 1 (paragraphs 0070-0073), Burzynski shows that when a female patient diagnosed with adenocarcinoma of the colon was administered a composition comprising a sterile solution of six amino acids, L-arginine, and riboflavin prior to treatment by chemotherapy with methotrexate and 5-fluorouracil, the patient did not experience the side effects typically associated with the chemotherapy treatment.

McCarthy *et al.* teach risk factors associated with mucositis in patients receiving 5-fluorouracil chemotherapy for cancer of the digestive tract. Oral mucositis is a dose-limiting toxicity of 5-fluorouracil and includes inflammation and ulceration of the oral mucosa and myelosuppression (abstract; p. 484, column 2). Although no direct relationship could be drawn, their results suggest that a lower neutrophil count is associated with the development of oral mucositis during therapy (p. 488, column 2, last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutryate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the different diluting agents available for use in medicinals, with the teachings of Burzynski, regarding a pharmaceutical composition comprising riboflavin, effectors of the urea cycle and amino acids, with the teachings of McCarthy *et al.*, regarding the risk factors associated with mucositis in patients receiving 5-fluorouracil chemotherapy for cancer of the digestive tract. Since Okuda *et al.* teach that riboflavin tetrapalmitate did not have vitamin B<sub>2</sub> activity as compared to riboflavin tetrabutryate when fed to rats while riboflavin-5'-monopalmitate showed signs of lower vitamin B<sub>2</sub> activity as compared to riboflavin-5'-monobutyrate when fed to rats, one would have been motivated to modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-laurate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Okuda *et al.*, that long chain tetra-esters of riboflavin exhibited no riboflavin activity while long chain mono-esters of riboflavin exhibited some riboflavin activity. Therefore, since Okuda *et al.* also teach that the tetra- and mono-butyrate esters of riboflavin showed the same activity as riboflavin, suggesting that shorter alkyl chain esters of riboflavin are better hydrolyzed, one would have been motivated to shorten the palmitate chain to a laurate chain, such as that taught by Yamabe *et al.* However, one would further modify the riboflavin trilaurate compound taught by Yamabe

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*et al.* to riboflavin-5'-monolaurate, as the teachings of Okuda *et al.* also suggests that with longer chain esters, the mono-ester compound is better hydrolyzed as compared to the tetra-ester compound, and therefore, would also likely be better hydrolyzed as compared to the tri-ester compound taught by Yamabe *et al.*

With regards to the combination of ethyl oleate in the composition, since Remington teaches that a variety of diluting agents can be added to medicinals and further indicates that prescribers have the opportunity to make their own prescriptions more acceptable to the patient since a large selection of diluting agents is available in a choice of colors and flavors, it would have been *prima facie* obvious for one of ordinary skill in the art to determine which carrier would be most appropriate for use in their composition depending on the compound's properties, intended mode of administration of the composition, and intended patient population.

It is noted that the Burzynski reference does not specifically teach the administration of ester analogs of riboflavin to cancer patients exhibiting the common side effects of chemotherapy. However, as described above in section [0001] of the claim rejections under 35 USC § 103, Okuda *et al.* teach that esters of riboflavin can be hydrolyzed to the natural riboflavin compound and thus exhibit activity similar to riboflavin. Therefore, esters of riboflavin can serve as functional substitutes for natural riboflavin when administered in a composition. Furthermore, it would have *prima facie* obvious to one of ordinary skill in that art that the enhanced lipophilicity of the riboflavin ester due to the presence of the alkyl chain would enhance its migration through lipid bilayers of cells, and thus its bioavailability. Therefore, as digestive tract catarrh is a

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risk factor of patients undergoing chemotherapy and riboflavin can alleviate the toxicity associated with a chemotherapy regimen, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the riboflavin compound taught by Burzynski with a riboflavin ester as Okuda *et al.* teach that esters of riboflavin are easily hydrolyzed to riboflavin.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

#### **Section [0005]**

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record), in view of Remington's The Science and Practice of Pharmacy (PTO-892, Ref. U) as applied to claims 12, 24, 25, 28 and 29, further in view of U.S. Patent No. 6,565,891 to Chandra (herein referred to as the '891 patent, of record).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103. The teachings of Remington were as described above in section [0002] of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.*, Okuda *et al.* and Remington differ from that of the instantly claimed invention in that the riboflavin ester is administered for treatment of ariboflavinosis and not for the treatment of persistent oral ulcer.

The Chandra '891 patent teaches a nutritional supplement for children that is most effective in optimizing health, increasing the immunity, and decreasing the

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instances and severity of infection, particularly among children (abstract). The importance of each of the component vitamins and minerals making up the nutritional supplement is described in detail. Of particular relevance, is the importance of riboflavin in the nutritional supplement. The '891 patent teaches that riboflavin participates in oxidation-reduction reactions in numerous metabolic pathways and in energy production via the respiratory chain (column 7, lines 22-31). It is used therapeutically to ameliorate ariboflavinosis resulting from diverse causes such as inadequate dietary intake, decreased assimilation, rare genetic defects in the formation of specific flavoproteins, hormonal disorders and after use of certain drugs. Symptoms indicating riboflavin deficiency include rough skin, angular stomatitis, cracked lips, and mouth ulcers.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutryrate and riboflavin tetrapalmitate, with the teachings of Remington, regarding the different diluting agents available for use in medicinals, with the teachings of the Chandra '891 patent, regarding the various symptoms of riboflavin deficiency. Since Okuda *et al.* teach that riboflavin tetrapalmitate did not have vitamin B<sub>2</sub> activity as compared to riboflavin tetrabutryrate when fed to rats while riboflavin-5'-monopalmitate showed signs of lower vitamin B<sub>2</sub> activity as compared to riboflavin-5'-monobutyrate when fed to rats, one would have been motivated to modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-laurate. One would have been motivated to combine the

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teachings in order to receive the expected benefit, as suggested by Okuda *et al.*, that long chain tetra-esters of riboflavin exhibited no riboflavin activity while long chain mono-esters of riboflavin exhibited some riboflavin activity. Therefore, since Okuda *et al.* also teach that the tetra- and mono-butyrate esters of riboflavin showed the same activity as riboflavin, suggesting that shorter alkyl chain esters of riboflavin are better hydrolyzed, one would have been motivated to shorten the palmitate chain to a laurate chain, such as that taught by Yamabe *et al.* However, one would further modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-monolaurate, as the teachings of Okuda *et al.* also suggests that with longer chain esters, the mono-ester compound is better hydrolyzed as compared to the tetra-ester compound, and therefore, would also likely be better hydrolyzed as compared to the tri-ester compound taught by Yamabe *et al.* Furthermore, as oral ulcers are a symptom of riboflavin deficiency, treatment of ariboflavinosis with a riboflavin ester would suffice to also treat oral ulcers.

With regards to the combination of ethyl oleate in the composition, since Remington teaches that a variety of diluting agents can be added to medicinals and further indicates that prescribers have the opportunity to make their own prescriptions more acceptable to the patient since a large selection of diluting agents is available in a choice of colors and flavors, it would have been *prima facie* obvious for one of ordinary skill in the art to determine which carrier would be most appropriate for use in their composition depending on the compound's properties, intended mode of administration of the composition, and intended patient population.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

#### **Section [0006]**

Claims 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 43-025506 to Yamabe *et al.* (IDS dated 8 June 2009), in view of journal publication by Okuda *et al.* (of record), in view of Remington's The Science and Practice of Pharmacy (PTO-892, Ref. U) as applied to claims 12, 24, 25, 28 and 29, further in view of journal publication by Stuchlík *et al.* (PTO-892, Ref. V), as evidenced by online publication entitled "Carrier/Fixed Oil Profiles" (PTO-892, Ref. W).

The teachings of Yamabe *et al.* and Okuda *et al.* were as described above in section [0001] of the claim rejections under 35 USC § 103. The teachings of Remington were as described above in section [0002] of the claim rejections under 35 USC § 103.

The combined teachings of Yamabe *et al.*, Okuda *et al.* and Remington do not teach that the composition administered in the method comprises camellia oil.

The teachings of Stuchlík *et al.* were as disclosed above in section [0002] of the claim rejections under 35 USC § 103.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Yamabe *et al.*, concerning riboflavin trilaurate, with the teachings of Okuda *et al.*, regarding the ariboflavinosis-curing effects of riboflavin-5'-monobutyrate and monopalmitate as compared to riboflavin tetrabutyrates and riboflavin tetrapalmitate, with the teachings of Remington, regarding the different

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diluting agents available for use in medicinals, with the teachings of Stuchlík *et al.*, regarding different vegetable oils used as pharmaceutical carriers. Since Okuda *et al.* teach that riboflavin tetrapalmitate did not have vitamin B<sub>2</sub> activity as compared to riboflavin tetrabutyrates when fed to rats while riboflavin-5'-monopalmitate showed signs of lower vitamin B<sub>2</sub> activity as compared to riboflavin-5'-monobutyrate when fed to rats, one would have been motivated to modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-laurate. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested by Okuda *et al.*, that long chain tetra-esters of riboflavin exhibited no riboflavin activity while long chain mono-esters of riboflavin exhibited some riboflavin activity. Therefore, since Okuda *et al.* also teach that the tetra- and mono-butyrate esters of riboflavin showed the same activity as riboflavin, suggesting that shorter alkyl chain esters of riboflavin are better hydrolyzed, one would have been motivated to shorten the palmitate chain to a laurate chain, such as that taught by Yamabe *et al.* However, one would further modify the riboflavin trilaurate compound taught by Yamabe *et al.* to riboflavin-5'-monolaurate, as the teachings of Okuda *et al.* also suggests that with longer chain esters, the mono-ester compound is better hydrolyzed as compared to the tetra-ester compound, and therefore, would also likely be better hydrolyzed as compared to the tri-ester compound taught by Yamabe *et al.*

With regards to the combination of ethyl oleate in the composition, since Remington teaches that a variety of diluting agents can be added to medicinals and further indicates that prescribers have the opportunity to make their own prescriptions

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more acceptable to the patient since a large selection of diluting agents is available in a choice of colors and flavors, it would have been *prima facie* obvious for one of ordinary skill in the art to determine which carrier would be most appropriate for use in their composition depending on the compound's properties, intended mode of administration of the composition, and intended patient population.

With regards to the combination of camellia oil in the composition, since Stuchlík *et al.* teach that olive oil and camellia oil is often used as a carrier in pharmaceutical formations and that the main components of olive oil and camellia oil are both oleic acid, it would have been *prima facie* obvious for one of ordinary skill in the art to substitute the olive oil in the riboflavin ester composition taught by Okuda *et al.* with camellia oil and still obtain similar predictable results. Furthermore, it is considered within the capabilities of one of ordinary skill in the art to optimize the amounts of diluting agent/carrier in the composition to obtain the most effective formulation.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

### **Conclusion**

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/  
Supervisory Patent Examiner, Art Unit 1623

SCARLETT GOON  
Examiner  
Art Unit 1623